

# **Paper IV**

ORIGINAL ARTICLE

## Breathing exercises with vagal biofeedback may benefit patients with functional dyspepsia

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### Abstract

**Objective.** Many patients with functional dyspepsia (FD) have postprandial symptoms, impaired gastric accommodation and low vagal tone. The aim of this study was to improve vagal tone, and thereby also drinking capacity, intragastric volume and quality of life, using breathing exercises with vagal biofeedback. **Material and methods.** Forty FD patients were randomized to either a biofeedback group or a control group. The patients received similar information and care. Patients in the biofeedback group were trained in breathing exercises, 6 breaths/min, 5 min each day for 4 weeks, using specially designed software for vagal biofeedback. Effect variables included maximal drinking capacity using a drink test (Toro<sup>®</sup> clear meat soup 100 ml/min), intragastric volume at maximal drinking capacity, respiratory sinus arrhythmia (RSA), skin conductance (SC) and dyspepsia-related quality of life scores. **Results.** Drinking capacity and quality of life improved significantly more in the biofeedback group than in the control group ( $p = 0.02$  and  $p = 0.01$ ) without any significant change in baseline autonomic activity (RSA and SC) or intragastric volume. After the treatment period, RSA during breathing exercises was significantly correlated to drinking capacity ( $r = 0.6$ ,  $p = 0.008$ ). **Conclusions.** Breathing exercises with vagal biofeedback increased drinking capacity and improved quality of life in FD patients, but did not improve baseline vagal tone.

**Key Words:** Biofeedback, breathing exercises, functional dyspepsia, vagal tone

### Introduction

Vagal activity is important in the regulation of the tone of the gastric wall. In response to a meal, the gastric musculature relaxes through vago-vagal reflexes to accommodate the meal without any increase in pressure. Low vagal tone [1] and impaired gastric relaxation [2] are often seen in patients with functional dyspepsia (FD), and epigastric discomfort is thought to be a consequence of inadequate reflex relaxation of the stomach wall musculature [3]. The relaxation impairment may be a consequence of anxiety and stress-induced vagal suppression, because anxiety and stress are associated with FD [4], and these psychological factors may impair gastric relaxation [5], antral motility [1] and vagal activity [1,6,7], whereas positive coping skills, such as a sense of humour, may reduce symptoms and morbidity [8].

Respiratory sinus arrhythmia (RSA) has been established as an index of parasympathetic (i.e. vagal) myocardial influence [9]. In healthy subjects, RSA increases with deep, calm breathing [10]. Alteration of vagal tone, using relaxation techniques controlling the breathing pattern, can be learned by biofeedback [11]. Biofeedback is an instrument-aided form of psychotherapy, where the patient can learn to control biological processes in the body; for instance by visualization of these responses. Biofeedback has been successfully employed in the treatment of irritable bowel syndrome (IBS) [12].

Because low vagal tone has been suggested as a mediating mechanism by which psychological factors induce dyspepsia in FD patients [1,7,13], we hypothesized that improvement in vagal tone would alleviate dyspepsia. The specific aims of the present

study were to investigate whether enhancement of vagal tone using breathing exercises and vagal biofeedback in patients with FD would improve parasympathetic activity and thereby beneficially influence drinking capacity, which is often impaired in FD patients [14–16], intragastric volumes and dyspepsia-related quality of life.

## Material and methods

### Subjects

The patients were recruited from the outpatient clinic at Haukeland University Hospital in Bergen, Norway. During a period of 36 months, 86 patients were screened for eligibility, 46 patients were excluded (13 refused to participate, 6 had moved too far away, 18 did not fulfil the Rome II criteria (diabetes mellitus 1, IBS 6, too few complaints 11), and 9 were excluded because they did not turn up at

appointments). Forty patients fulfilling the Rome II criteria were included in the study (Figure 1, Table I). All patients had undergone recent normal gastric endoscopic investigations.

### Experimental procedure

The participants were examined after an overnight fast at the start (visit 1) and at the end (visit 2) of a 4-week period. The examinations at visit 1 and visit 2 followed the same procedure. First, questionnaires were filled in. Thereafter RSA was measured while the individuals were breathing normally (5 min), sitting in a chair leaning slightly backwards at an angle of 120°. Then 100 ml meat soup was ingested every minute until maximal drinking capacity, followed by scanning for 3-dimensional ultrasonography and assessment of RSA for 5 min. At this point at visit 1, the patients were randomized into a biofeedback group and a control group.

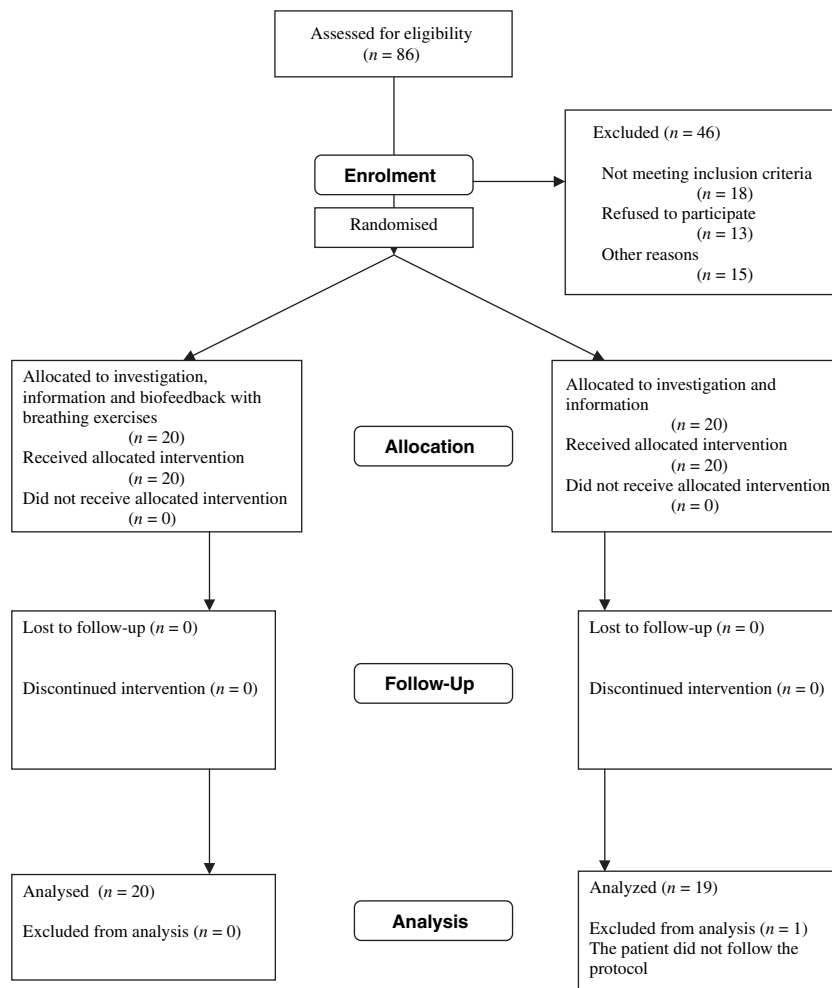


Figure 1. Participant flow and follow-up. Eighty-six patients were assessed for eligibility. During enrolment, 46 patients were excluded. The 40 patients included were randomized into two groups; 20 patients in each group. None were lost during follow-up or analysis, but one patient in the group allocated to investigation and information was excluded from the analysis because of lack of compliance.

Table I. Descriptive data of the two groups: number of patients and gender, mean scores  $\pm$ SD of age, BMI, volumes and questionnaires assessed at visit 1.

	Biofeedback group	Control group	<i>p</i> -values
Number of patients	20	20	
Gender (F/M)	15/5	17/3	
Mean age (years)	36.8 $\pm$ 14.4	33.8 $\pm$ 10.1	0.4
BMI (kg/m <sup>2</sup> )	23.37 $\pm$ 3.8	22.8 $\pm$ 3.4	0.6
Drinking capacity (ml)	705.0 $\pm$ 243.8	661.1 $\pm$ 352.4	0.7
Intragastric volume (ml)	520.3 $\pm$ 194.4	429.3 $\pm$ 222.3	0.2
Gastric emptying (%)	26.7 $\pm$ 18.7	33.5 $\pm$ 17.5	0.2
SF-NDI (score)	24.7 $\pm$ 7.6	22.9 $\pm$ 8.2	0.5
EPQ-N (score)	4.5 $\pm$ 3.1	5.5 $\pm$ 3.2	0.3
Telic Dominance Scale (score)			
Serious-mindedness	4.0 $\pm$ 1.8	4.8 $\pm$ 1.2	0.09
Planning orientation	5.9 $\pm$ 2.2	6.6 $\pm$ 2.7	0.3
Arousal avoidance	6.9 $\pm$ 2.5	5.8 $\pm$ 2.1	0.1
SHQ-6 (score)	18.9 $\pm$ 2.3	19.8 $\pm$ 1.9	0.2

Abbreviations: BMI = body mass index; SF-NDI = Short-Form Nepean Dyspepsia Index; EPQ-N = Neuroticism Subscale of the Eysenck Personality Questionnaire; SHQ-6 = Sense of Humour Questionnaire with six questions.

#### Biofeedback group

Those in the biofeedback group were informed about FD and started training in breathing exercises with vagal biofeedback using a specially designed software program. RSA was measured concomitantly with breathing exercises and vagal biofeedback. Visit 1 and visit 2 lasted about 1.5 h in this group. During the first week of the treatment period, the patients practised breathing exercises (6 breaths/min 5 min daily) using a portable computer with vagal biofeedback software. Correct breathing technique was ensured before the last three weeks were completed without the use of a computer. The patients listened to calm guitar music during breathing exercises during the 4 weeks (“In Wonder”, from the album “Passion & Grace” composed and performed by Govi). The music lasted for 5 min and the beat of the rhythm was 60, helping the subjects to keep the 6 breaths/min. The investigator called the patients once a week during the treatment period to confirm good compliance, lasting 3–6 min each time.

#### Control group

Those in the control group were informed about FD, and came back 4 weeks later for visit 2 without having had any contact with the investigators in the meantime. At the end of visit 2, those who wanted to were trained in biofeedback and breathing exercises, for later use at their own initiative. Visit 1 and visit 2 lasted for about one hour each.

#### Biofeedback

“Freeze-Framer” is computer software developed by the Institute of HeartMath in Boulder Creek, California. It monitors beat-by-beat changes in heart rate with an electronic sensor placed on the subject’s second finger on the non-dominant hand. The Freeze-Framer records the degree of smoothness or jaggedness of the heart rhythm and, based on a mathematical algorithm, assigns a score. A smoother heart rhythm pattern indicates a balanced nervous system, and it is possible to increase the smoothness of the heart rhythm pattern through relaxation, using breathing exercises. With the correct breathing technique, a warm-air balloon starts to float upwards. With deterioration in performance, the balloon loses height and even lands on the ground if performance does not improve. Evaluation of performance, or entrainment ratio, is summarized in a red, blue and green column (low, medium and high entrainment ratio, respectively) using a percentage scale.

The training criterion in this study was to attain, in total, a high and medium entrainment ratio of at least 70%. If the training criterion was not reached, the patients had to practise using the Freeze Framer once a week until the training criterion was reached or the 4 weeks had been completed.

#### Test meal

The test meal was a commercially available meat soup, 4 kcal/100 ml (Toro clear meat soup, Rieber & Son A/S, Bergen, Norway); 500 ml contained 1.8 g protein, 0.9 g fat, 1.1 g carbohydrate and non-soluble seasoning (0.4 g/l). The pH of the soup varied between 5.4 and 5.7, and the osmolarity was 350 mOsm/kgH<sub>2</sub>O. The soup was boiled and then cooled to 37°C. The ingestion rate was 100 ml/min until maximal drinking capacity.

#### Questionnaires

The Norwegian versions of the “Short-form Nepean Dyspepsia Index” (SF-NDI) [17], “Sense of Humour Questionnaire” (SHQ-6) [18], “Telic Dominance Scale” [19] and the Neuroticism Subscale of the “Eysenck Personality Questionnaire” (EPQ-N) [20] were completed at visit 1. At visit 2, the SF-NDI was filled in once more. In addition, the patients in the biofeedback group scored their appreciation of the music on the first and the last day of treatment.

The SF-NDI is a disease-specific measure of quality of life, with 10 questions divided into five subscale scores (tension, interference with daily activities, eating/drinking, knowledge/control, work/

study) and one total score. Each question has five options giving 1–5 points (1 = not at all, 5 = extremely), thus the total score range is 10–50. Mean total score is  $13.5 \pm 6.8$  in the general Norwegian population ( $n = 70$ ) [21].

The SHQ-6, which measures the patients' sense of humour, ability to discover humorous hints and situations, and attitude to humorous others, comprises 6 questions, each with a 4-step scoring format (1–4) and, when summarized, they provide the total SHQ-6 score ranging from 6 (low sense of humour) to 24, with a normal value of 15.5 in urban areas.

The "Telic Dominance Scale" is used to analyse serious-mindedness, planning orientation and arousal avoidance by means of 42 questions, with 14 questions for each subscale. A mean or normal value of serious-mindedness is  $6.4 \pm 1.9$ , planning orientation is  $5.6 \pm 2.1$  and arousal avoidance is  $6.4 \pm 2.3$ .

In the EPQ-N, neuroticism is scored through 12 Yes/No questions. Answering "Yes" to any of the questions gives 1 point, and the possible range of scores is 0–12. Normal values vary with gender and age from 4.14 (old men) to 6.7 (young women). In our subjects (mostly women, mean age 35 years) normal values would be  $5.5 \pm 2.9$ .

The scoring of appreciation of the music was done using a 10-step scoring format (1 = I strongly dislike the music, and 10 = I liked the music very much).

#### *Vagal tone*

Vagal nerve function was evaluated non-invasively using a computerized polygraph (Synectics® software and polygraph, Medinor®, Oslo, Norway). The R-R interval in the ECG was registered by the computer and transformed into beats per minute. Three Ag/AgCl electrodes were attached to the thorax; 2–3 cm under the right and left clavicle bones and at the left 5th intercostal space in the mid-clavicular line. Respiratory movements were recorded simultaneously using a pressure-sensitive sensor attached to the thorax. Recordings were stored in digital format on a computer hard disk for off-line scoring, calculating the average of peak-to-trough changes of heart rate within six successive respiratory cycles [6,9,10].

#### *Skin conductance*

Sympathetic tone was indexed by skin conductance (SC) and evaluated non-invasively using a computerized polygraph (Synectics software and polygraph, Medinor). SC, expressed in micro Siemens ( $\mu\text{S}$ ), was recorded by the electro dermal constant current method. Two Ag/AgCl electrodes were attached on the palmar side of the third and fourth

interphalanges on the non-dominant hand. Recordings were stored in digital format on a computer hard disk for off-line scoring. SC was assessed concomitantly with RSA.

#### *Ultrasonography*

Three-dimensional ultrasonography (using System Five Ving Med A/S, Horten, Norway) with a 3.5 MHz curved array probe was performed at maximal satiety using previously evaluated methods [22]. The recordings were stored, and all intragastric volume measurements were performed blindly after study completion, and double checked by two investigators.

Gastric emptying was defined as the fraction (%) of the meal emptied from the stomach during the test meal ((drinking capacity minus intragastric volume)  $\times$  100/drinking capacity).

#### *Ethics approval*

The study was approved by the Regional Committee for Medical Research Ethics and conducted in accordance with the revised Declaration of Helsinki. All participants gave written, informed consent to participate in the trial.

#### *Statistical analysis*

In this exploratory study we sought to evaluate the effect of vagal biofeedback and breathing exercises on drinking capacity in patients with FD. The number of patients needed in each group was calculated as follows: an increase in drinking capacity of 200 ml would be clinically relevant. Supposing a standard deviation of 200 ml, a difference of this magnitude would be statistically significant (power 85%) with 20 patients in each group.

Patients were randomly allocated to a biofeedback group or control group, using a computer-generated randomization list. The group identity of each patient was placed in numbered envelopes, hidden from the investigator who enrolled the patients and assigned them to the two groups.

Descriptive statistics are expressed as mean values  $\pm$  standard deviation (SD), if not otherwise stated. Two-way repeated measures ANOVA with Bonferroni post-tests was used to determine the overall effects. Pairwise comparison was done by paired *t*-test, or Wilcoxon's signed-rank test, when appropriate. We analysed the average difference between the two groups of paired observations and the variability of these differences according to Altman [23]. Multiple regression analyses were used to test scores from psychological measures as potential sources of confounding influences upon

differences between the biofeedback group and the control group. A  $p$ -value  $\leq 0.05$  (alpha criterion) was chosen as the level of statistical significance using two-tailed tests. All statistical calculations and graphic designs were performed using commercially available software (Prism 4.0 and SPSS 14.0 for Windows). None of the subjects dropped out of the study, but a few values were missing because of technical problems. One patient in the control group did not comply with the protocol, as he decided at visit 2 to “break all records” in drinking capacity, and he was excluded from the data concerning drinking capacity and volume measurements.

## Results

Overall effects using repeated measures ANOVA were found for drinking capacity, intragastric volumes, gastric emptying and quality of life, but not for RSA and SC (Table II).

### Drinking capacity

There was increased drinking capacity in the biofeedback group (visit 1: Table I,  $n=20$ , visit 2:  $827.5 \pm 308.4$  ml,  $n=20$ ) ( $p=0.008$ ), but no significant change in the control group (visit 1: Table I,  $n=19$ , visit 2:  $668.4 \pm 371.4$  ml,  $n=19$ ) ( $p=0.7$ ). The change in drinking capacity (visit 2 minus visit 1) was significantly different between the groups (biofeedback group:  $122.5 \pm 185.3$  ml; control group:  $7.4 \pm 85.2$  ml) (Figure 2).

### Intragastric volumes

In the repeated measures ANOVA analysis, 3 patients in the biofeedback group and 5 patients in the control group were excluded because of missing data. In the biofeedback group, intragastric volumes increased, but not significantly (visit 1: Table I,  $n=18$ , visit 2:  $534.9 \pm 210.0$  ml,  $n=19$ ) ( $p=0.3$ ). In

the control group, intragastric volumes increased significantly (visit 1: Table I,  $n=18$ , visit 2:  $486.8 \pm 173.4$  ml,  $n=16$ ) ( $p=0.02$ ). However, the change in intragastric volumes (visit 2 minus visit 1) was not significantly different between the two groups (biofeedback group:  $38.6 \pm 149.6$  ml,  $n=17$ ; control group:  $80.5 \pm 114.4$  ml,  $n=15$ ) (Figure 2).

### Gastric emptying

From the first to the second visit, there was a slowing of emptying in the control group (visit 1: Table I,  $n=18$ , visit 2:  $21.7 \pm 19.9\%$ ,  $n=16$ ) ( $p=0.02$ ). In the biofeedback group there was an insignificant increase in emptying (visit 1: Table I,  $n=18$ , visit 2:  $31.8 \pm 19.7\%$ ,  $n=19$ ) ( $p=0.4$ ). The change in gastric emptying (visit 2 minus visit 1) was significantly different between the groups (biofeedback group:  $4.0 \pm 17.8\%$ ,  $n=17$ ; control group:  $-12.5 \pm 18.8\%$ ,  $n=15$ ) (Figure 2).

### Quality of life

The patients in the biofeedback group had lower scores after the treatment period compared with before treatment (visit 1: Table I,  $n=19$ , visit 2:  $21.2 \pm 7.1$ ,  $n=20$ ) ( $p=0.01$ ), whereas patients in the control group had a non-significant increase in scores from the first (Table I,  $n=20$ ) to the second visit ( $23.7 \pm 9.0$ ,  $n=20$ ) ( $p=0.4$ ). The decrease in score (visit 2 minus visit 1) was significantly greater in the biofeedback group ( $-3.4 \pm 5.4$ ,  $n=19$ ) compared with the control group ( $0.8 \pm 4.1$ ,  $n=20$ ) (Figure 2).

Subanalysis showed that knowledge/control improved in both the biofeedback group (visit 1:  $3.9 \pm 1.9$ ,  $n=19$ , visit 2:  $3.3 \pm 1.2$ ,  $n=20$ ,  $p=0.03$ ) and the control group (visit 1:  $4.0 \pm 1.9$ ,  $n=20$ , visit 2:  $3.4 \pm 1.5$ ,  $n=20$ ,  $p=0.04$ ), but there was no difference between the groups (biofeedback group:  $-0.6 \pm 1.2$ ; control group:  $-0.6 \pm 1.2$ ) ( $p=1.0$ ).

Table II.  $F$ - and  $p$ -values for repeated measures ANOVA and number of subjects in the analyses. The group factor describes whether there are any differences between the biofeedback group and the control group. The time factor describes any differences between the first and second visit. Interaction investigates whether the differences observed are more than just chance variations.

	Interaction		Group factor		Time factor		$n$
	F	P	F	P	F	P	
Drinking capacity	6.1	0.02	1.0	0.3	7.8	0.008	40
Intragastric volume	0.8	0.4	2.3	0.1	6.3	0.02	32
Gastric emptying	5.1	0.03	0.3	0.6	1.0	0.3	32
SF-NDI	7.4	0.01	0.01	0.9	2.8	0.1	39
RSA (baseline)	2.2	0.2	0.8	0.4	1.8	0.2	39
SC (baseline)	2.3	0.1	1.5	0.2	0.1	0.7	40

Abbreviations: SF-NDI = Short-Form Nepean Dyspepsia Index, a disease-specific quality of life questionnaire; RSA = respiratory sinus arrhythmia; SC = skin conductance.

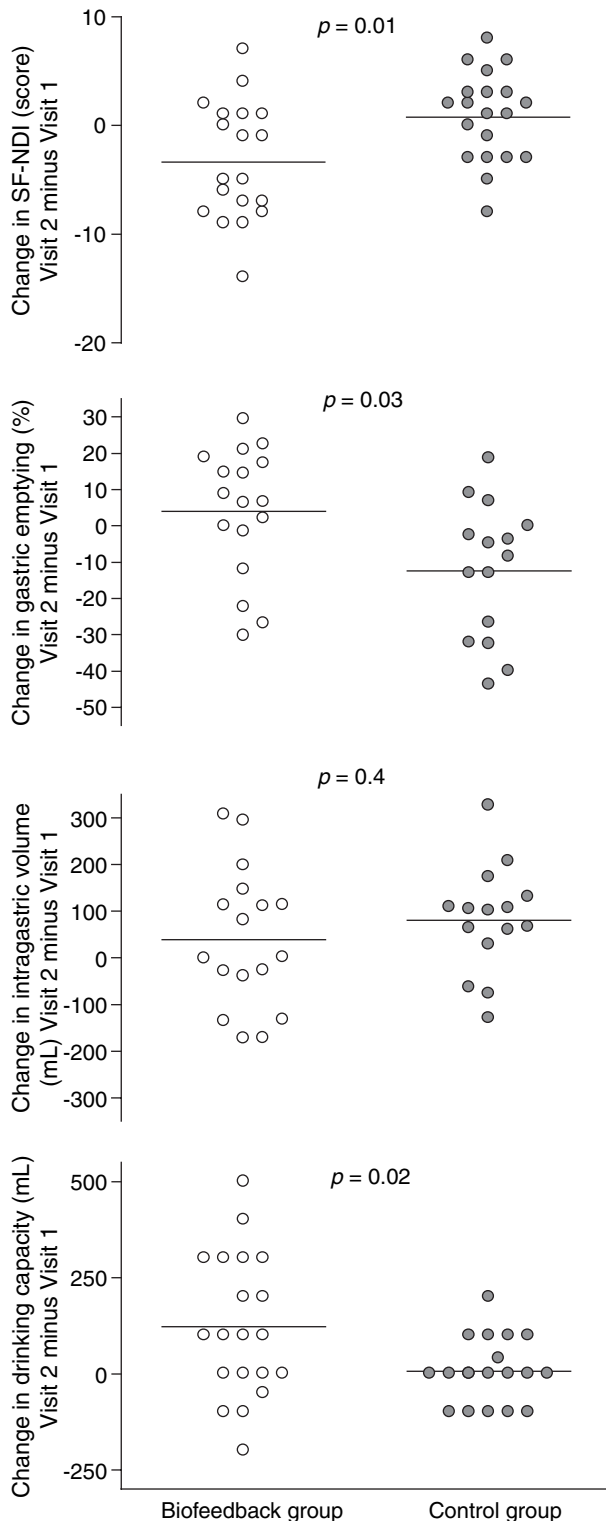


Figure 2. Change in drinking capacity (ml), intragastric volume (ml), gastric emptying (%) and quality of life (SF-NDI score) (visit 2 minus visit 1) in the biofeedback group and the control group. SF-NDI = Short-form Nepean Dyspepsia Index.

However, eating/drinking only improved in the biofeedback group (visit 1:  $6.5 \pm 2.1$ ,  $n = 19$ , visit 2:  $5.2 \pm 1.8$ ,  $n = 20$ ,  $p = 0.007$ ; control group: visit 1:  $4.9 \pm 1.4$ ,  $n = 20$ , visit 2:  $5.5 \pm 1.9$ ,  $n = 20$ ,  $p = 0.1$ ),

and the improvement was significantly greater than in the control group (biofeedback group:  $-1.3 \pm 1.8$ ; control group:  $0.6 \pm 1.6$ ) ( $p = 0.002$ ).

#### Respiratory sinus arrhythmia

RSA increased significantly during breathing exercises ( $p < 0.0001$ ). There was no significant change in baseline RSA (Table III) and no significant change from fasting to postprandial, either in the biofeedback group (visit 1:  $p = 0.9$ , visit 2:  $p = 0.4$ ), or in the control group (visit 1:  $p = 0.3$ , visit 2:  $p = 0.7$ ).

RSA during breathing exercises was significantly positively correlated to drinking capacity only at visit 2 ( $r = 0.6$ ,  $p = 0.008$ ), not at visit 1 ( $r = 0.4$ ,  $p = 0.1$ ).

Four patients did not reach the training criterion within the first week. Two of them reached the training criterion within the end of the four weeks.

#### Skin conductance

SC increased significantly after the meals in both the biofeedback group (visit 1:  $p = 0.03$ , visit 2:  $p = 0.007$ ) and the control group (visit 1:  $p = 0.0006$ , visit 2:  $p < 0.0001$ ), but there was no significant change in SC during breathing exercises, which were performed after the test meal (visit 1:  $p = 0.7$ , visit 2:  $p = 0.4$ ). SC did not change significantly from one visit to the other (Table III).

#### Psychological and music questionnaires

Descriptive statistics of the psychological questionnaire scores are reported in Table I ( $n = 40$ ). There was no change in appreciation of the music in the biofeedback group from the start ( $6.6 \pm 2.5$ ) to the end of the study ( $6.1 \pm 2.9$ ) ( $p = 0.5$ ) ( $n = 20$ ).

#### Effects of psychological differences

A series of hierarchical regression analyses were performed to test the confounding effects of potentially biased psychological differences between the treatment groups upon dependent variables. In these analyses, the effect of age was entered in the first step. It is well known that serious-mindedness, planning orientation and arousal avoidance tend to increase with age [24], and such psychological characteristics may influence the rigour of compliance in behavioural intervention. Moreover, if random differences in psychological characteristics between patients across the two groups influenced data outcome, these differences might mistakenly be ascribed to treatment differences rather than to differences in psychological traits. Therefore, the group factor was included in the second step, and the psychological variables were included in the third

Table III. Mean values of respiratory sinus arrhythmia and skin conductance at baseline, postprandially and during breathing exercises in the biofeedback group and the control group.

	RSA			SC		
	Baseline (fasting)	Postprandial	Breathing exercises	Baseline (fasting)	Postprandial	Breathing exercises
<b>Biofeedback group</b>						
Visit 1 (A1)	4.6±2.3	4.5±2.5	16.3±10.1	3.0±5.0	5.3±6.6	5.7±5.8
Visit 2 (A2)	4.6±3.2	5.2±3.3	15.9±8.1	4.1±5.1	7.7±6.4	8.2±7.2
<i>p</i> -values	0.9	0.3	0.4	0.3	0.1	0.06
<b>Control group</b>						
Visit 1 (B1)	6.0±2.9	5.3±2.1		6.2±7.2	9.3±6.7	
Visit 2 (B2)	4.8±2.4	4.9±2.1		4.4±4.5	8.4±5.0	
<i>p</i> -values	0.06	0.4		0.3	0.5	
<i>p</i> -values						
A1 versus B1	0.09	0.3		0.1	0.07	
A2 versus B2	0.9	0.7		0.9	0.7	

Abbreviations: RSA = respiratory sinus arrhythmia (beats per minute, mean ±SD,  $n = 19$  for the biofeedback group's visit 2 postprandial and visit 2 breathing exercises,  $n = 20$  for all other RSA values); SC = skin conductance ( $\mu\text{S}$ , mean ±SD,  $n = 20$  in each group).

step of the regression analysis. This approach allowed assessment of the impact of psychological differences upon change in SF-NDI, RSA, SC, drinking volume and gastric emptying from the first to second visit, after controlling for the effects of age and the group factor upon these dependent variables. No significant overall effect of psychological measures upon dependent variables was found. However, planning orientation tended to be positively correlated, with an increase in gastric emptying from the first to the second visit ( $t = 2.03$ ,  $p = 0.051$ ) in both groups. The results from pairwise correlations indicated that serious-mindedness, planning orientation and arousal avoidance increased with age also in this sample of subjects ( $r$ -values: 0.29, 0.28, 0.68;  $p$ -values: 0.03, 0.04, 0.004, respectively).

## Discussion

Impaired drinking capacity has previously been found to be a characteristic feature of patients with FD [14–16]. This type of impairment has been attributed to poor cholinergic (vagal) control of gastric accommodation [1,7,13]. Consistent with our hypothesis, breathing exercises aiming to improve RSA (vagal tone) significantly improved drinking capacity and dyspepsia-related quality of life in our patients with FD. RSA during breathing exercises was positively correlated to drinking capacity solely after the treatment period, not before, suggesting that learning the correct breathing technique is important. However, although vagal tone improved during breathing exercises, “baseline” vagal tone remained unchanged, suggesting no persistent effect on cholinergic control of cardiac rhythmic activity. The

mechanism by which biofeedback treatment exerted its beneficial effects is therefore not clear.

Lack of maintenance of the improvement in vagal tone might be due to overly short-lasting treatments (5 min a day). Short treatment periods were chosen in order to improve compliance. A previous study [25], using 1-h sessions once a week with daily home exercises (thermal feedback with breathing exercises + a relaxation program) for 8 weeks, has shown longer-lasting clinical improvement. Leahy et al. [12] reported some benefit of treating patients with IBS using 30-min sessions with mental relaxation once a week for 4 weeks, along with daily home exercises. Denis [26] claimed that the duration of feedback sessions cannot be standardized because of the variability of subjects' ability to learn, their motivation, the pathology and the investigators' practices. Nevertheless, we find our results with 5-min periods of breathing exercises encouraging and would suggest further research to determine whether longer treatment periods are preferable.

In a previous study, using the same low-caloric test meal, enhancement of gastric vagal activity by insulin-induced hypoglycaemia increased drinking capacity and gastric emptying [27]. However, the enhanced efferent vagal activity to the stomach (as measured by pancreatic polypeptide) was not associated with enhanced cardiac vagal activity (as measured by RSA) [27]. Likewise, in a small, open study in patients with congestive heart failure, the Freeze-Framer was used in eight 75-min sessions over a period of 10 weeks and showed improvements in emotional coping and functional capacity, but without any persistent increase in heart rate variability [28]. Thus, the increased drinking capacity in



our biofeedback group might be due to mechanism other than increased cardiac vagal activity.

In the present study, quality of life scores improved significantly in the biofeedback group compared with the control group. Subanalysis showed that it was only for the eating/drinking subscale that the improvement was significant. Being included in a study improved scores for the subscale knowledge/control, independently of group identity. When adding vagal biofeedback, eating capacity and the ability to enjoy eating and drinking were improved.

Quality of life is influenced by psychological factors such as anxiety and depression, which are common in FD and might be part of its pathophysiology [29]. Experimentally induced anxiety inhibits gastric accommodation and increases symptoms after a test meal [5]. Respiratory control evokes feelings of peacefulness and relaxation, i.e. the opposite of anxiety [11,30]. Hence, the effects of our feedback therapy in FD could be due to anxiety relief and not necessarily the effects of improved vagal tone.

Patients with FD do not constitute a uniform group. In our study, most of the patients did not have particularly low vagal tone as compared with those in other studies using the same methods [7,31]. In future projects using vagal biofeedback and breathing exercises, it might be advantageous to select patients with low vagal tone, as they would possibly benefit more from the treatment. It seems important to learning the correct breathing technique, because after 4 weeks of practice, there was a strong relationship between vagal tone during breathing exercises and drinking capacity.

Slow, deep breathing is found to prevent gastric dysrhythmias, as well as decreasing the symptoms of motion sickness and increasing the parasympathetic nervous system activity as measured by RSA [32]. Performing breathing exercises while drinking the test meal was not attempted in our study.

Soothing music has the power to lower blood pressure, reduce heart rate and respiration, reduce stress, reduce subjective anxiety and induce a feeling of well-being and relaxation [33,34], whereas rousing music increases blood pressure, heart rate and respiration and evokes feelings of vigour and tension [33]. Music preference may increase with repetition [35], and even rousing music may then induce relaxation and reduce tension [36]. Favourite music lowers subjective tension, but has no effect on heart rate and blood pressure [33]. We used calm guitar music, which can be classified as soothing. The unfamiliar piece was repeated once every day for 4 weeks. Although increased preference could not be documented, we had the impression that our music induced relaxation and pleasure.

Vagal tone increased during breathing exercises. Because of the design of our study, we cannot make a distinction between effects that are attributable to music, vagal biofeedback or breathing exercises. However, music and breathing were synchronized in our study. Vagal biofeedback was manipulated by breathing exercises, and vagal tone increases with respiration alone [10]. Thus, it seems likely that respiration is the most important factor responsible for the increase in vagal tone.

We found it impossible to administer placebo treatment and to blind the patients to whether they received active treatment or not. To minimize placebo effect differences between groups, we chose to have a biofeedback group receiving active treatment in addition to conventional information and investigation, and a control group receiving conventional information and investigation, as investigation and information itself might induce improvement of this condition.

However, the main result is that the procedure, including breathing exercises with vagal biofeedback, seems to help patients with FD. This treatment is safe, easy to learn and is not time consuming. Therefore, it can be applied in a hectic, clinical daily practice. However, more research is needed to find the optimal “dose” of the treatment, and to study the mechanisms behind the biofeedback-assisted improvement in drinking capacity and quality of life among FD patients.

## References

- [1] Hausken T, Svebak S, Wilhelmsen I, Haug TT, Olafsen K, Pettefson E, et al. Low vagal tone and antral dysmotility in patients with functional dyspepsia. *Psychosom Med* 1993; 55:12–22.
- [2] Gilja OH, Hausken T, Wilhelmsen I, Berstad A. Impaired accommodation of proximal stomach to a meal in functional dyspepsia. *Dig Dis Sci* 1996;41:689–96.
- [3] Coffin B, Azpiroz F, Guarner F, Malagelada JR. Selective gastric hypersensitivity and reflex hyporeactivity in functional dyspepsia. *Gastroenterology* 1994;107:1345–51.
- [4] Haug TT, Wilhelmsen I, Berstad A, Ursin H. Life events and stress in patients with functional dyspepsia compared with patients with duodenal ulcer and healthy controls. *Scand J Gastroenterol* 1995;30:524–30.
- [5] Geeraerts B, Vandenberghe J, Van OL, Gregory LJ, Aziz Q, Dupont P, et al. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. *Gastroenterology* 2005;129:1437–44.
- [6] Grossman P, Svebak S. Respiratory sinus arrhythmia as an index of parasympathetic cardiac control during active coping. *Psychophysiology* 1987;24:228–35.
- [7] Haug TT, Svebak S, Hausken T, Wilhelmsen I, Berstad A, Ursin H. Low vagal activity as mediating mechanism for the relationship between personality factors and gastric symptoms in functional dyspepsia. *Psychosom Med* 1994;56: 181–6.

- [8] Svebak S, Sondenaa K, Hausken T, Soreide O, Hammar A, Berstad A. The significance of personality in pain from gallbladder stones. *Scand J Gastroenterol* 2000;35:759–64.
- [9] Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. *J Appl Physiol* 1983;54:961–6.
- [10] Hjelland IE, Hausken T, Svebak S, Olafsson S, Berstad A. Vagal tone and meal-induced abdominal symptoms in healthy subjects. *Digestion* 2002;65:172–6.
- [11] Reyes del Paso GA, Godoy J, Vila J. Self-regulation of respiratory sinus arrhythmia. *Biofeedback Self Regul* 1992; 17:261–75.
- [12] Leahy A, Clayman C, Mason I, Lloyd G, Epstein O. Computerised biofeedback games: a new method for teaching stress management and its use in irritable bowel syndrome. *J R Coll Physicians Lond* 1998;32:552–6.
- [13] Berstad A. Functional dyspepsia: a conceptual framework. *Gut* 2000;47 Suppl 4:iv3–iv4.
- [14] Boeckxstaens GE, Hirsch DP, van den Elzen BD, Heisterkamp SH, Tytgat GN. Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. *Gastroenterology* 2001;121:1054–63.
- [15] Hjelland IE, Ofstad AP, Narvestad JK, Berstad A, Hausken T. Drink tests in functional dyspepsia: which drink is best? *Scand J Gastroenterol* 2004;39:933–7.
- [16] Jones MP, Hoffman S, Shah D, Patel K, Ebert CC. The water load test: observations from healthy controls and patients with functional dyspepsia. *Am J Physiol Gastrointest Liver Physiol* 2003;284:G896–G904.
- [17] Talley NJ, Verlinden M, Jones M. Quality of life in functional dyspepsia: responsiveness of the Nepean Dyspepsia Index and development of a new 10-item short form. *Aliment Pharmacol Ther* 2001;15:207–16.
- [18] Svebak S. The development of the Sense of Humor Questionnaire: From SHQ to SHQ-6. *Humor: Int J Humor Res* 1996;9:341–61.
- [19] Murgatroyd S, Rushton C, Apter M. The development of the Telic Dominance Scale. *J Personality Assess* 1978;42: 519–28.
- [20] Eysenck S, Eysenck H, Barrett P. A revised version of the psychoticism scale. *Person Individ Diff* 1985;6:21–9.
- [21] Arslan G, Lind R, Olafsson S, Florvaag E, Berstad A. Quality of life in patients with subjective food hypersensitivity: applicability of the 10-item short form of the Nepean Dyspepsia Index. *Dig Dis Sci* 2004;49:680–7.
- [22] Tefera S, Gilja OH, Olafsdottir E, Hausken T, Hatlebakk JG, Berstad A. Intra-gastric maldistribution of a liquid meal in patients with reflux oesophagitis assessed by three dimensional ultrasonography. *Gut* 2002;50:153–8.
- [23] Altman DG. Two groups of paired observations. In: Altman DG, editor. *Practical statistics for medical research*. Boca Raton, Florida: Chapman & Hall/CRC; 1999. pp 189–91.
- [24] Ruch W. Temperament, Eysenck's PEN system, and humor-related traits. *Humor. Int J Humor Res* 1994;7:209–44.
- [25] Ford MR, Stroebel CF, Strong P, Szarek BL. Quieting response training: long-term evaluation of a clinical biofeedback practice. *Biofeedback Self Regul* 1983;8:265–78.
- [26] Denis P. Methodology of biofeedback. *Eur J Gastroenterol Hepatol* 1996;8:530–3.
- [27] Hjelland IE, Oveland NP, Leversen K, Berstad A, Hausken T. Insulin-induced hypoglycemia stimulates gastric vagal activity and motor function without increasing cardiac vagal activity. *Digestion* 2005;72:43–8.
- [28] Luskin F, Reitz M, Newell K, Quinn TG, Haskell W. A controlled pilot study of stress management training of elderly patients with congestive heart failure. *Prev Cardiol* 2002;5:168–72.
- [29] Haug TT, Svebak S, Wilhelmsen I, Berstad A, Ursin H. Psychological factors and somatic symptoms in functional dyspepsia. A comparison with duodenal ulcer and healthy controls. *J Psychosom Res* 1994;38:281–91.
- [30] Fasko D Jr, Osborne MR, Hall G, Boerstler RW, Kornfeld H. Co-meditation: an exploratory study of pulse and respiration rates and anxiety. *Percept Mot Skills* 1992;74: 895–904.
- [31] Hveem K, Svebak S, Hausken T, Berstad A. Effect of mental stress and cisapride on autonomic nerve functions in functional dyspepsia. *Scand J Gastroenterol* 1998;33:123–7.
- [32] Jokerst MD, Gatto M, Fazio R, Stern RM, Koch KL. Slow deep breathing prevents the development of tachygastric and symptoms of motion sickness. *Aviat Space Environ Med* 1999;70:1189–92.
- [33] Iwanaga M, Moroki Y. Subjective and physiological responses to music stimuli controlled over activity and preference. *J Music Ther* 1999;36:26–38.
- [34] Knight WE, Rickard NS. Relaxing music prevents stress-induced increases in subjective anxiety, systolic blood pressure, and heart rate in healthy males and females. *J Music Ther* 2001;38:254–72.
- [35] Bartlett D. Effect of repeated listenings on structural discrimination and affective response. *J Res Music Ed* 1973;21:302–17.
- [36] Iwanaga M, Ikeda M, Iwaki T. The effects of repetitive exposure to music on subjective and physiological responses. *J Music Ther* 1996;33:219–30.